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A COMPARISON OF THE HISTODYNAMICS OF SEBACEOUS GLANDS AND EPIDERMIS IN MAN: A MICROANATOMIC AND MORPHOMETRIC STUDY*

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TISSUE GROWTH AND REPLACEMENT

In spite of obvious differences in structure and physiology, sebaceous glands are biologically similar to epidermis. Like the epidermis, they are composed of "retaining cells" (Birbeck and Mercer, 1961) which, unlike secretory cells, accumulate the product they synthesize inside their cytoplasm until they die. The population of sebaceous cells, like that of the epidermis, is organized into a three-compartment system. Each compartment has its own distinct functional and topographic features: (1) a stem cell population whose mitotic activity restores cells lost from the system; (2) an expanding compartment, where differentiation and perhaps mitosis take place; and (3) a terminal compartment where the cells complete their maturation and are eliminated.

The maintenance of these tissues is believed to depend on a reciprocally synchronized balance between cell supply, differentiation, and elimination. The term steady balance denotes a hypothetical tissue kinetic state whereby, during differentiation, lost cells are replaced by new cells in an orderly fashion according to equal input and output timing. Theoretically, such a model should result in a stable tissue structure, but actually the model is more imaginary than real, as is indicated below.

Mitotic activity in sebaceous glands is mainly focal, occurring mostly in buds or aggregates of undifferentiated cells from the walls of the excretory ducts and from the periphery of the acini (Montagna, 1963a,b). As these buds grow into sebaceous units, differentiation begins in their centers. Replacement thus takes place from a succession of cell clusters in the acini. Sebaceous acini, therefore, are transient or unstable structures, which undergo variation in shape and volume according to the amount and distribution of mitotic activity.

A similar mechanism of self-maintenance occurs in the epidermis. Our studies (Tosti et al., 1959; Tosti, 1968) indicate that the only way epidermal cell clusters, originating from focal mitoses in the stem compartment, can expand is by forming buds that extend into the dermis and cause the rete ridges to multiply and/or elongate. Following maturation, these cells form the epidermal flakes of keratinized stratum corneum. The flakes are shed as the location and mitotic activity of the rete ridges constantly change.

Therefore, in both sebaceous glands and epidermis, the main kinetic units are cell clusters which originate one after another from groupings of stem cells which are simultaneously entering mitosis. This finding, plus the occurrence of random mitoses in both sebaceous glands and epidermis, makes it most difficult to construct a precise model of tissue kinetics on the basis of static studies. Therefore, the hypothetical model of a steady tissue balance that has been used to calculate turnover time in tissue is open to question. The histologic features of sebaceous acini suggest that differentiation is not necessarily closely associated with cell multiplication during which cell clusters might be expected to differentiate synchronously. Differentiation appears to spread by many intermediate stages from the center of the clusters toward the periphery, an indication that cell input and output vary within the system.

DIFFERENTIATION

The outstanding feature of sebaceous differentiation is the progressive increase in the size of cells. When cells in serial histologic sections were measured and the cell volume was calculated according to the stage of cell differentiation, five distinct morphologic cell stages emerged (Fig. 1): (a) undifferentiated, potential sebaceous cells; (b,c,d) cells in early, advanced, and full differentiation; (e) mature cells. Figure 2 shows histograms of the average cell volumes at each of these stages in normal sebaceous glands, actively regenerating glands, and sebaceous follicles. During differentiation, the volume of sebaceous cells increases by a factor of 100 to 150; this is an index of lipid synthesis during sebaceous transformation. The volume of keratinocytes also increases during differentiation, but not to the same degree as in sebaceous cells. Figure 3 shows a histogram in which the average cell volumes in sebaceous follicles and hyperplastic epidermis are compared. The significance of these differences becomes apparent when the dry mass of the cytoplasm is considered.

Microradiographic analysis (Tosti and Fazzini, 1964) can determine whether the increase in volume is due to an increased concentration of cytoplasmic products. Differentiating keratinocytes show a progressive increase in cytoplasmic x-ray absorption. In differentiating sebaceous cells, on the other hand, the level of x-ray absorption remains unchanged; when lipids are extracted from the cells in the reticulated cytoplasm, x-ray absorption actually decreases. Sebaceous cells do not concentrate their product of differentiation but

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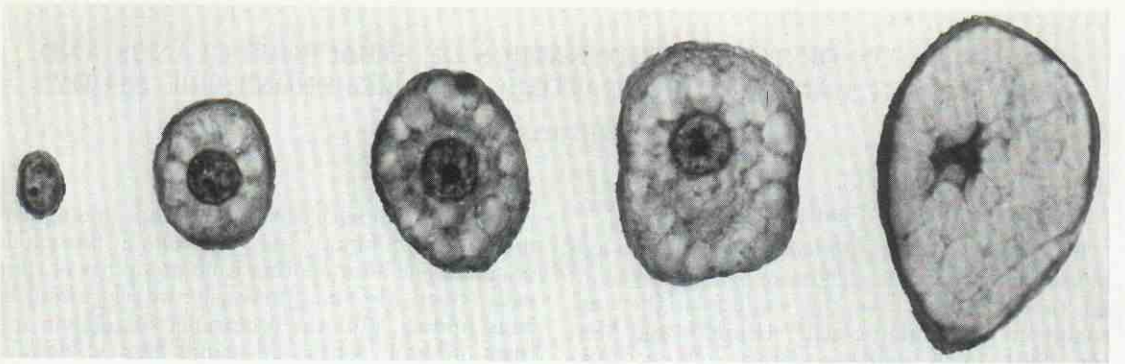

FIG. 1: Five stages in the differentiation of sebaceous cells.

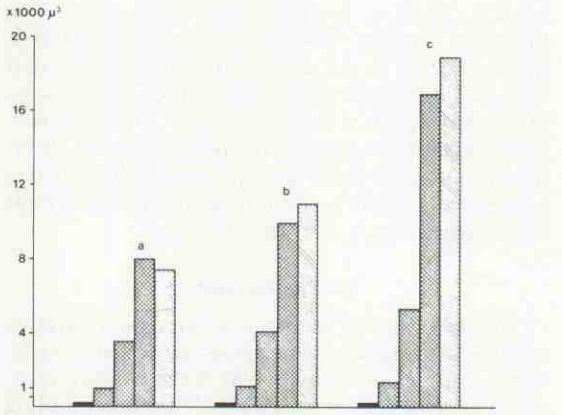

FIG. 2

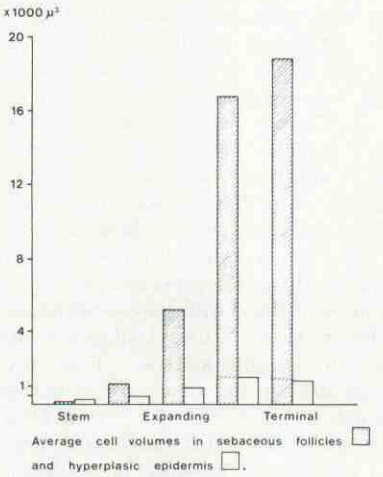

FIG. 3

maintain a linear relation between dry mass and volume: therefore, the concentration of cytoplasmic dry mass as differentiation advances is greater in keratinocytes than in sebaceous cells. The dry weight per volume is lower in sebaceous glands

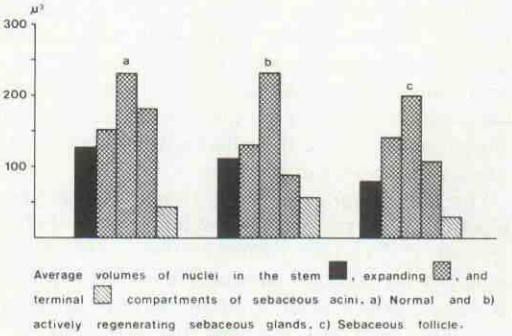

FIG. 4

than in keratinocytes because of (1) the low ratio of dry mass/volume of the cytoplasm, and (2) the low specific weight of lipids compared to that of proteins.

Changes in the dry mass of nuclei also differ in the two cell types. The nuclei of both keratinocytes and sebaceous cells increase moderately in volume during differentiation and shrink in late maturation (Fig. 4). In sebaceous cells, however, the nuclei retain strong x-ray absorption, whereas in differentiating keratinocytes the x-ray absorption of nuclei, in contrast to the strong absorption of their nucleoli, is decreased. In sebaceous cells, then, the dry mass of the nuclei does not change whereas in keratinocytes it decreases. Scanning electron microscopy confirms this; in sebaceous cells the nuclei bulge out, but in keratinocytes most nuclei resemble depressed areas around elevated nucleoli (Figs. 5a,b, 6a,b).

The levels of photoabsorption also distinguish sebaceous cells from keratinocytes (Tosti et al., 1971). Contact images of sebaceous acini at 2580 Å UV show strong absorption in the peripheral undifferentiated cells. This absorption decreases as the cells differentiate (Fig. 7a,b). This indicates that the aromatic compounds, unsaturated linkages, and other resonating structures, which act as chromophores at the wavelength used, decrease in concentration in the cytoplasm of differentiating sebaceous cells. Keratinocytes, however, show an

increase in photoabsorption under the same conditions, an indication that the resonating structures increase during maturation.

Photoabsorption over a range of 5000–9000 Å is also different in sebaceous cells and keratinocytes. Infrared photomicrographs of unstained sections (Tosti et al., 1969) show that the cytoplasm of keratinocytes is cyanic (the infrared response) whereas that of sebaceous cells is orange and magenta (the visible light response). In contrast, nuclei and cell membranes are cyanic in sebaceous cells but not in keratinocytes.

During differentiation, sebaceous cells attain greater dimensions than keratinocytes but do not concentrate the same amount of dry mass and chromophores in their cytoplasm as in keratinocytes.

SEBACEOUS GLANDS AND EPIDERMIS: VOLUME VERSUS MASS

Compared with keratinocytes, differentiating sebaceous cells have a relatively low ratio between mass and volume. This indicates that the size and volume of sebaceous acini reflect more the stage of

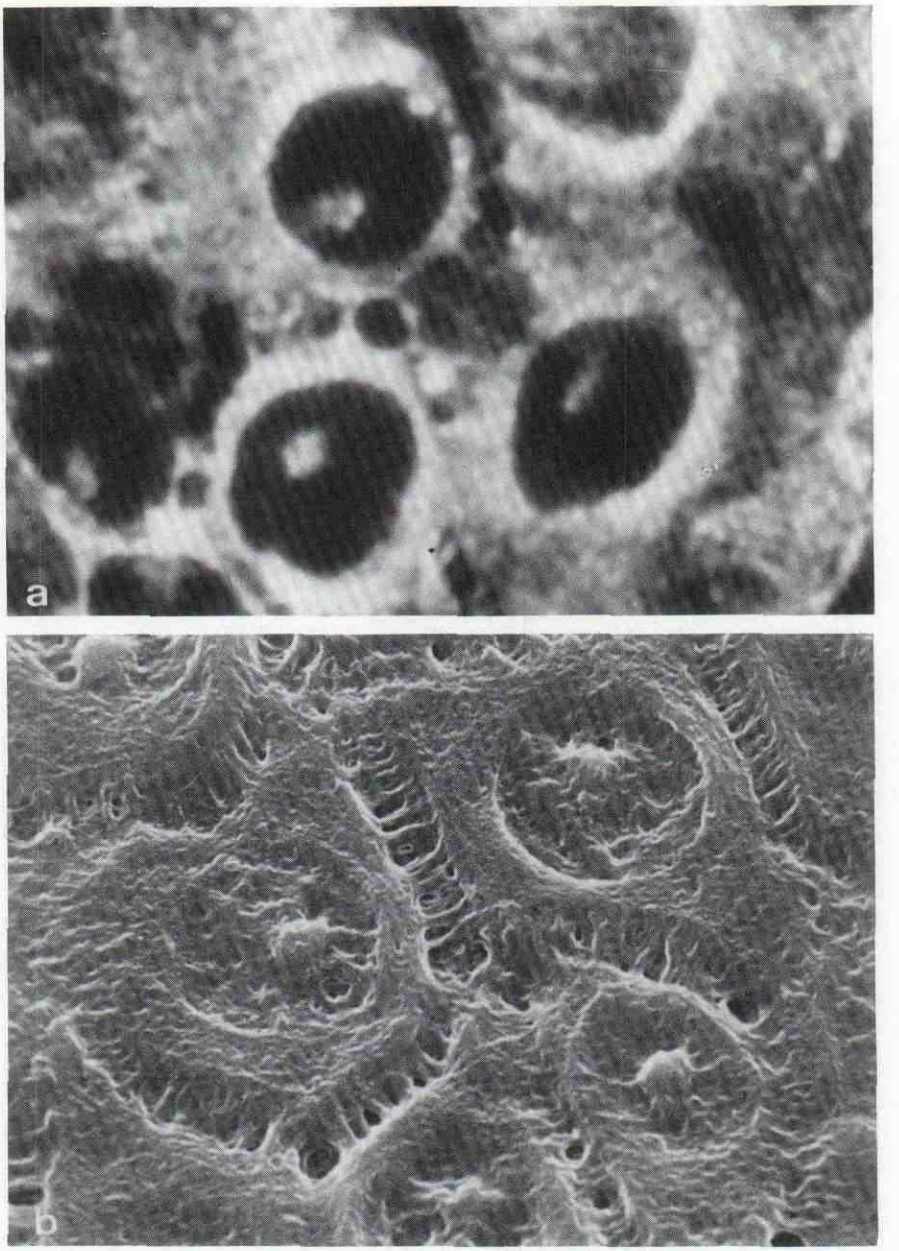

FIG. 5: (a) X-ray image of differentiating epidermal cells showing strong absorption by cytoplasms and nucleoli and low absorption by nuclei. (b) Scanning electron micrograph showing elevated cytoplasmic areas and nucleoli and depressed nuclei.

cell differentiation than the actual number of cells. This becomes apparent if one considers the space occupied in the acini by the expanding stem cells in the terminal compartment. The sebaceous component of skin from the nape of a middle-aged man constitutes 30 percent of the volume of each section. In measurements carried out on x-ray images and on serial histologic sections of the faces and napes of adult male subjects, sebaceous glands constituted 21–36 percent of the tissue volume, excluding the hypodermis. In the same specimens, only 5.5–7.3 percent of the volume was represented by epidermis.

In terms of the efficiency/volume ratio, the epidermis is a far more compact tissue than the bulkier sebaceous glands. However, volume may have functional significance in promoting kinetic conversion. As the acini expand during growth, a peripheral tension force is generated, the vectorial result of which may be centripetal, forcing mature sebaceous cells to be extruded into the ducts. The concomitant increases or decreases of tension during the growth or depletion of acini may result in a self-regulation of the tissue kinetics. Tissue tension may also control the kinetics of the epidermis. Buds growing on the undersurface give it a larger

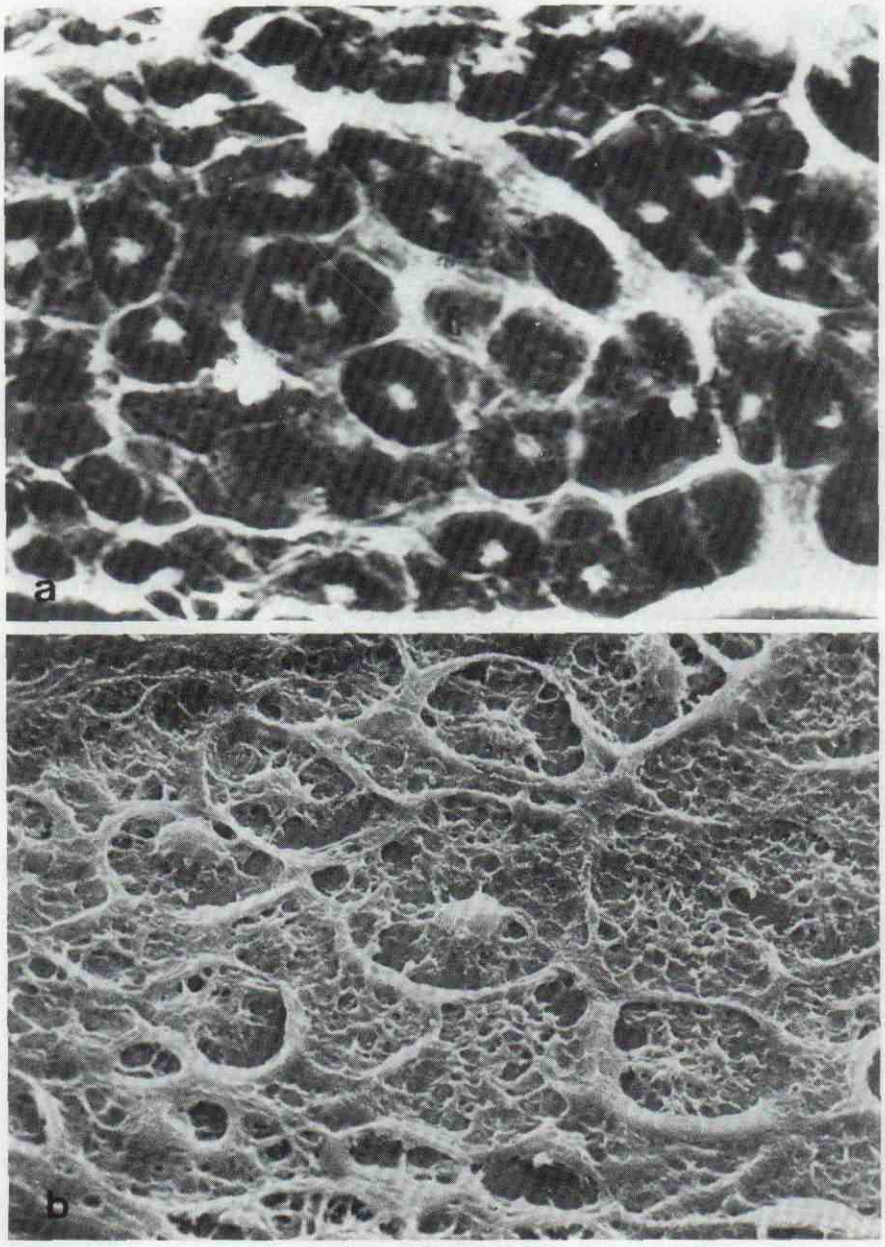

FIG. 6: (a) X-ray absorption by nuclei of differentiating sebaceous cells. (b) Scanning electron micrograph of differentiating sebaceous cells, showing prominent nuclei.

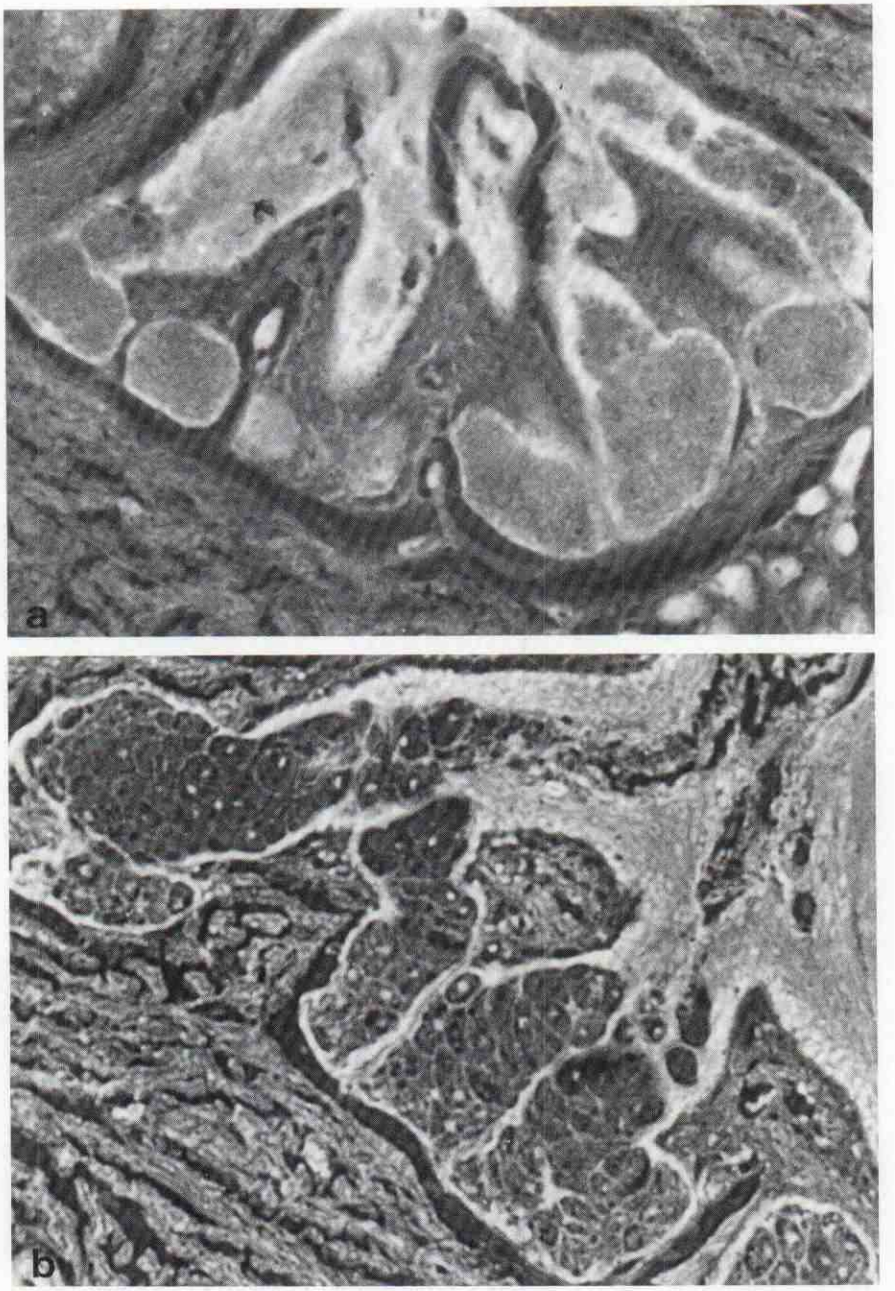

FIG. 7: (a) Contact image of a sebaceous gland exposed to 2580 Å UV showing a decrease of the absorption of UV as the cells differentiate. (b) This photograph shows the pattern of UV absorption when lipids are extracted from the cells.

area than that on the outer surface. Therefore, a force may be developed which generates outward pressure, varying according to the changes in the ratio of the inner and outer surfaces.

CONCLUSIONS

Sebaceous glands and epidermis appear to be controlled by similar kinetic forces. In both, development proceeds through three distinct cell compartments; in both, tissue renewal is the result of focal mitotic activity that generates cell clusters; in both, the products of differentiation are stored and disposed within the cells that form them.

There are differences, however, in some of the physical properties of sebaceous glands and keratinocytes. Keratinocytes progressively concentrate their products of differentiation but do not undergo as great an increase in cell size as sebaceous cells. As differentiation advances, cytoplasmic photoabsorption increases in keratinocytes but not in sebaceous cells. The ratio of efficiency/volume in sebaceous glands is lower than that in the epider-

mis since, as a result of lipid accumulation, enlargement is greater than during keratinization. Thus, sebaceous glands are bulky machines that occupy more space than their function warrants. Perhaps it is this increase in volume that generates the peripheral tension forces which extrude mature sebaceous cells and acts as a regulating mechanism.

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